Annals of Oncology **10** *(Suppl. 1): S87-S92, 1999.*

Consensus statements

Advanced epithelial ovarian cancer: 1998 consensus statements

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Summary

Background: During an international workshop held in September 1998, a group of specialists in the field of ovarian cancer reached consensus on a number of issues with implications for standard practice and for research of advanced epithelial ovarian cancer.

Methods: Five groups of experts considered several issues which included: biologic factors, prognostic factors, surgery, initial chemotherapy, second-line treatment, the use of CA 125, investigational drugs, intra-peritoneal treatment and high-dose chemotherapy. The group attempted to arrive at answers to questions such as: Are there prognostic factors, which help to identify patients who will not do well with current therapy? What is the current best therapy for advanced ovarian carcinoma? What directions should research take in advanced ovarian cancer? These issues were discussed in a plenary meeting.

Results: One of the major conclusions drawn by the consensus committee was that in previously untreated advanced ovarian cancer, cisplatin plus paclitaxel has been shown to be superior to previous standard therapy with cisplatin plus cyclophosphamide (level I evidence). However, for many patients, carboplatin plus paclitaxel is a reasonable alternative because of toxicity and convenience considerations. Most participants felt that the benefits in terms of toxicity for the paclitaxel-carboplatin are such that its widespread adoption at this stage is justified. Until mature survival data are available a minority of investigators would recommend continued use of cisplatin plus paclitaxel, specifically for those patients with advanced disease with the best prognostic characteristics.

For future clinical research in this area, new end points for randomised clinical trials, together with a new Trials Network, are proposed.

Key words: CA 125, consensus, management, ovarian cancer, prognostic factors, second-line treatment, surgery

Introduction

During a 3-day international workshop held in September 1998 consensus was reached by the authors of this article on a number of issues with implications for standard practice and for research into the treatment of advanced epithelial ovarian cancer. Issues discussed included: biologic factors, prognostic factors, surgery, initial chemotherapy, second-line treatment, the use of CA 125, investigational drugs, intra-peritoneal treatment, high-dose chemotherapy and designs for future trials.

When relevant the level of evidence is provided in this paper. Evidence-based medicine combines clinical expertise and the best available evidence from systematic research to aid decision making. Levels of evidence can be graded from I to V, with level I, the strongest, coming from large randomised controlled trials.

Prognostic factors

Clinical recommendations

There are currently no factors used to select specific therapy. We have many prognostic factors, but we urgently require factors that have predictive significance (a predictive factor gives information useful in selection of patients likely to benefit from a specific treatment).

Research recommendations

The use of clinico-pathological factors is extremely important for the stratification of patients within clinical trials. It is recommended that for all future prognostic analyses the following details should be included in advanced stage patients: age, performance status, histology, tumour grade (degree of differentiation), stage, residual disease (microscopic or none vs. macroscopic).

Molecular markers
Several "molecular markers" have been shown to be of potential prognostic importance and warrant further study, although none have, as yet, conclusively been shown to be of independent prognostic significance. These include: oncogene products (her-2/neu, p21), suppressor gene products (p53, p16, pRB) and measures of drug sensitivity (Pgp, LRP, MRP, GST, BAX). Firm evidence on the independent prognostic value of novel molecular markers can only be achieved by the use of standardised methodology. Large prospective databases are required; ideally in the setting of randomised clinical trials. These studies should all include appropriate multivariate analysis, which includes known clinico-pathological factors. Studies in the neoadjuvant setting would be of particular value where these putative factors can be associated with chemosensitivity.

Surgery in advanced disease

Clinical recommendations

Definitive conclusions regarding the role of surgical procedures in advanced ovarian cancer were made difficult by the lack of randomised studies providing level I evidence in this area. Nevertheless, radical surgical cytoreduction was regarded as standard primary treatment. It was agreed that surgical resectability and ultimate prognosis are influenced by tumour biology and technical expertise.

Definitions
International agreement about the terminology for surgical procedures in advanced ovarian cancer is important. The following standard definitions for various operative interventions are recommended:

1. Primary cytoreductive surgery: an operation to remove as much of the tumour and its metastases as possible before subsequent therapy is instituted.
2. Interval cytoreductive surgery: an operation performed in patients after a short course of induction chemotherapy, usually two or three cycles of chemotherapy, to remove as much primary and metastatic disease as possible in order to facilitate response to subsequent chemotherapy and to improve survival.
3. Second-look surgery: an exploratory laparotomy to assess the cancer status of a patient performed in women who are clinically free of disease (including normal CA 125 and no radiologic evidence of disease) after the completion of a defined course of chemotherapy, typically six cycles.
4. Secondary cytoreductive surgery: an operation performed on patients who have either persistent disease at the completion of a planned course of chemotherapy or who subsequently experienced clinical relapse.
5. Palliative secondary surgery: an operation performed in patients who manifest symptoms and signs of progressive disease (e.g. gastrointestinal obstruction), in an effort to relieve symptoms for a minimally acceptable period.

Primary cytoreductive (debulking) surgery
Primary cytoreductive surgery should be the standard of care in advanced ovarian cancer, especially in stage III disease. The goal of cytoreductive surgery should be no or minimal residual disease at the end of the operation.
The role of cytoreductive surgery in FIGO stage IV is controversial but it was agreed that patients with pleural effusion only, a supraclavicular node or a single cutaneous metastasis can be treated as stage III disease. Extensive debulking is most likely of no benefit in patients with liver or lung metastases. Alternatively, neoadjuvant chemotherapy is an acceptable alternative to primary cytoreductive surgery in stage IV disease (see below).

Interval cytoreductive (debulking) surgery
It was generally agreed that the term intervention surgery should no longer be used because all types of surgery after the initial operation are intervention procedures.

A significant survival benefit for interval surgery has been demonstrated in one prospective randomised trial [1]. For this reason, many investigators agree that the performance of an interval debulking is an acceptable approach in women who did not or could not have a successful primary debulking operation (reduction of disease to less than 1 cm). Interval cytoreductive surgery is considered appropriate in patients whose disease is responding or stable (non-progressive) during induction chemotherapy. It should be noted however, that the key trial of this approach antedated the introduction of paclitaxel in induction chemotherapy and the results may therefore not be necessarily applicable.

Second-look laparotomy
We recommend no change in the prior recommendations [2]. Second-look laparotomy may be used as part of treatment protocols where informed consent is obtained, but should not be used as part of routine standard practice.

Secondary cytoreductive (debulking) surgery
For clinical purposes two groups of patients can be recognised, those with persistent disease at the completion of chemotherapy (no treatment-free interval) and those who relapse after a treatment-free interval. Most secondary cytoreductive surgeries are done for localised recurrences. Previous analyses have shown that optimal candidates for secondary cytoreductive surgery can be identified using predictive factors at the time of relapse [3]. These include tumours that relapse 12 months or longer from the completion of chemotherapy, those tumours that were responsive to primary chemotherapy, a high performance status, and a potential for complete resection based on pre-operative evaluation.

Palliative surgery
The decision regarding palliative surgery should be made as part of a multi-disciplinary evaluation of the patient. In general, surgery should be kept to a minimum and correction of intestinal obstruction should be performed in patients who appear most likely to benefit from such a surgery, for example indolent tumour growth, tumours that

have been chemosensitive, and minimal carcinomatosis at prior laparotomy or large bowel obstruction only. One would anticipate that patients who undergo such procedures would live for several months or longer.

Research recommendations

Neoadjuvant chemotherapy followed by surgery
An alternative to primary cytoreductive surgery is the administration of neoadjuvant therapy. In neoadjuvant chemotherapy patients with "localised tumour" are treated with systemic treatment before surgical treatment, using the presenting tumour mass as a biologic marker of responsiveness to the drugs. As the issue of the optimal therapy of stage IV disease is unresolved, we recommend that prospective clinical trials should be undertaken to compare primary cytoreductive surgery followed by chemotherapy with neoadjuvant chemotherapy; this is currently being studied in a randomised trial of the European Organisation for Research and Treatment of Cancer (EORTC) and of the Medical Research Council in the UK (MRC).

Secondary cytoreductive (debulking) surgery
The precise role of secondary surgical cytoreduction either at the completion of induction chemotherapy or at the time of relapse is unknown and clinical trials should address the value of this procedure. At present one such study of the EORTC investigates the benefit of surgery in patients with a relapse more than 12 months after chemotherapy (the LAROCSON study; Late Relapse of Ovarian Cancer Surgery Or Not).

Laparoscopy
This approach for treatment evaluation in ovarian cancer is not standard, however it may be an acceptable alternative in a research setting in selected patients. The use of the laparoscope in ovarian cancer is currently being studied. If laparoscopy is performed to determine resectability or as an interval or second-look procedure, it should be done as an "open" operation, i.e. with the option to proceed to laparotomy.

Initial therapy

Clinical recommendations

Paclitaxel plus cisplatin
There was uniform consensus that the standard approach to the management of patients with advanced ovarian cancer should consist of an attempt at cytoreductive surgery followed by combination chemotherapy with a taxoid and a platinum compound (unless there are contraindications on medical grounds). This recommendation was based upon level one evidence of two large prospective randomised trials which established that a combination of cisplatin plus paclitaxel was superior to cyclophosphamide plus cisplatin in patients with advanced ovarian cancer and applies to both optimally and suboptimally debulked patients [4, 5]. Superiority was evident in response rates, time-to-progression, and a clinically important improvement in overall survival. Whereas in both trials cisplatin was administered at a dose of 75 mg/m^2, paclitaxel was administered in a different dose and infusion time. In the first trial of the Gynecologic Oncology Group (GOG), paclitaxel was administered as a 135 mg/m^2 24-hour infusion while in the second trial paclitaxel was administered as a 175 mg/m^2 3-hour infusion. While the therapeutic advantages for the paclitaxel/platinum combinations were essentially identical, there were significant differences in toxicity. The 3-hour infusion of paclitaxel was associated with a higher degree of peripheral neuropathy, and it was proposed that when the paclitaxel plus cisplatin combination is used, it should be administered according to the GOG guidelines [4].

Paclitaxel plus carboplatin
There was also a general consensus that the combination of carboplatin plus paclitaxel was an acceptable alternative regimen for previously untreated patients with advanced disease. Three large prospective randomised trials comparing cisplatin plus paclitaxel versus carboplatin plus paclitaxel have been completed and mature results from these trials will shortly be forthcoming [6, 7, 8]. Already, from the 800-patient AGO trial, it is apparent that carboplatin plus paclitaxel has significantly less toxicity with an improvement in overall quality of life compared to treatment with 3-hour paclitaxel plus cisplatin. With a median follow-up of almost two years there was no statistically significant difference in progression-free survival between the two arms. It was the general recommendation that the results of the three trials should be pooled and a meta-analysis performed to increase statistical validity of the comparison. Until mature survival data are available, some (a minority of) investigators would recommend continued use of cisplatin plus paclitaxel specifically for those patients with advanced disease with the best prognostic characteristics. Others felt that the benefits in terms of toxicity for the paclitaxel-carboplatin combination are such that its widespread adoption at this stage is justified.

The choice of the carboplatin plus paclitaxel combination also remains to be defined. In the GOG studies, paclitaxel was used as a 175 mg/m^2 3-hour dose with carboplatin at an AUC of 7.5. In the Netherlands-Danish trial, paclitaxel was administered as a 175 mg/m^2 3-hour infusion and carboplatin at an AUC of 5, whereas in the AGO trial, paclitaxel was administered as a 185 mg/m^2 3-hour infusion and carboplatin at an AUC of 6. Prospective randomised trials have failed to demonstrate that there is a clinically significant advantage for dose escalation of carboplatin of AUC greater than 5 [9, 10].

Duration of therapy
Another major issue addressed was the number of cycles of therapy to be given and timing of therapy with regard to interval debulking surgery. Most studies have used 6 cycles of paclitaxel plus a platinum compound and there is no evidence that additional treatment provides any benefit with regard to survival. However, there was consensus that prospective randomised trials are needed in order to estab-

lish whether maintenance therapy with a paclitaxel-based regimen following induction therapy with 6 cycles is of benefit.

Role of anthracyclines
There was uniform agreement that the role of anthracyclines in ovarian cancer was worthy of further research. Improved survival of doxorubicin-treated patients in several meta-analyses [11, 12] provided the rationale for the ongoing trials in Europe of paclitaxel and carboplatin versus paclitaxel, epirubicin and carboplatin. Until these trials are completed, however, there was agreement that anthracyclines should not routinely be used in combination with paclitaxel and a platinum compound for initial treatment.

High-dose chemotherapy
There is no established role for high-dose chemotherapy with peripheral stem cell transplantation in any subset of patients with advanced ovarian cancer. Any such treatment should only be given within prospective randomised trials comparing high-dose therapy to conventional regimens. Possible roles for high dose chemotherapy might be as consolidation for complete or near complete remissions or as part of the initial induction regimen in patients with small volume disease.

Intraperitoneal therapy
There was uniform consensus that intraperitoneal chemotherapy should not be considered to be standard therapy at this point. Additional prospective randomised trials of intraperitoneal paclitaxel and cisplatin are justified based on earlier phase III trials [13, 14].

Role of CA 125
The tumour marker CA 125 currently plays a very important role in individual patient management. It is an accurate early indicator of treatment failure during front line therapy. Use and interpretation of CA 125 levels may be complicated by surgery, removal of third spaces fluids and the administration of allogenic monoclonal antibodies. Single determinations of CA 125 may be misleading.

Research recommendations

New drugs in first line combinations
A number of new drugs have proven activity in refractory disease, and feasibility trials of first line combinations (incorporating the new drug with paclitaxel and a platinum compound) are underway. These include antimetabolite (gemcitabine), topoisomerase I inhibitors (topotecan), topoisomerase II inhibitors (etoposide) and a novel polyetylene glycol coated liposomal doxorubicin (Doxil). In order to facilitate their evaluation we propose the following plan:

1. A pre-set minimum level of activity should be agreed for those patients with measurable-evaluable disease in exploratory trials. An overall clinical response rate of 70% is one option.
2. Each of the new drug options should be tested individually, i.e. in randomised phase III trials with only one variable, in which standard therapy comprises paclitaxel/carboplatin (or cisplatin). The experimental arm should comprise a 3 drug combination, either with the 3 drugs delivered together, or delivered sequentially (with the exception of the interesting new agent Herceptin (a recombinant humanised anti-HER2 antibody), that requires to be given concurrently with chemotherapy). The precise experimental regimen should depend on individual (biochemical) considerations for the drug in question.
3. These randomised phase III trials could have progression-free survival as their primary end point, could comprise perhaps 300-400 patients, and be conducted as part of a collaborative network of Trials Groups (see below).

Duration of therapy
Duration of therapy should be a high priority for future trials, since earlier trials including cisplatin have not satisfactorily addressed this issue for other drugs, particularly paclitaxel. Patients with advanced ovarian cancer should be treated with (standard) 6 courses of paclitaxel-carboplatin (or cisplatin), and those whose disease has responded to treatment could then be randomised to receive additional treatment e.g.: no further therapy, 3-6 courses of paclitaxel plus carboplatin, or 6 months of weekly injections of paclitaxel.

Such a trial will require a large number of patients, and may be appropriate for a new collaborative framework (see below).

Intraperitoneal chemotherapy
On the basis of one positive randomised clinical trial and of another which showed a trend to benefit, i.p. treatment represents an area of legitimate investigation [13, 14]. Randomised trials of i.p. treatment as first line or consolidation are justified using chemotherapy and/or biological agents. Patients with > 1 cm residual disease should not receive i.p. treatment but patients with minimal (< 1 cm) residual disease are potential candidates for i.p. therapy.

Significant morbidity can be associated with delivery of i.p. treatment; it is therefore important in trials to assess this morbidity carefully. Particular attention needs to be paid to the expertise of those who place and care for the catheters.

Trials network
In order to facilitate the above clinical research above, we propose a new network of current national groups. For new drug trials, several of these groups could ideally initiate trials at the same time. The same control arm and same end point assessment (progression-free survival) could be used. Data would be shared, and it would then be possible to “pick a likely winner”. That trial would then be enlarged by collaborative effort, and overall survival would become the end point in this definitive large-scale trial. At this stage, provision must be made to make the new drug available to patients on the control arm when they relapse.

Another possibility for a large scale trial of the new drug would be to include it in the framework of “duration

of therapy" trials above, i.e. to examine it's potential given for 6 courses after 6 courses of conventional therapy.

Stratification and end point assessment in trials
In the past, several groups have approached patients with minimal or bulk residual disease with separate/different clinical trial questions. There was general consensus that in the future (with the possible exception of those with no residual disease after initial surgery) patients should all be treated together in the same phase III trials for initial treatment, with stratification before randomisation.

We propose a new definition of progression-free survival, which is the major end point of the initial randomised phase III trials described above.

Patients would be described as having progressive disease on follow-up if they fulfil two of the following three criteria:

1. symptoms suggestive of disease, e.g. characteristic abdominal pain, distension, etc.
2. a rising CA 125 level (confirmed on at least two samples, using Rustin criteria) [15].
3. radiological or clinical evidence of a new lesion.

For those patients whose disease initially was not associated with an elevated CA 125, progression may be accepted on the basis of only one criterion, (1) or (3), according to individual circumstances.

Therapy of refractory and relapse disease

Clinical recommendations

Patients can benefit from second-line therapy but patients with refractory and relapsed disease are incurable and therefore any therapeutic manoeuvre should be regarded as palliative. The likelihood of benefit from second-line therapy must be balanced against the potential toxicity of the treatment. Parameters have been retrospectively evaluated that predict for both response and survival to second-line therapy. Patients who are likely to benefit from chemotherapy are those with good performance status, relatively small residual disease (< 5 cm), long treatment free interval, serous histology and a low number of sites of disease. It was generally agreed that in clinical practice the length of the treatment-free interval should influence selection of second-line treatment. It is worthwhile specifying three groups of patients. Those with:

1. tumour progression while on initial treatment or after a treatment-free interval of less than 4 months (refractory disease)
2. a treatment-free interval between 4-12 months (intermediate group)
3. a treatment-free interval of more than 12 months (sensitive recurrent disease).

Refractory disease
Patients who have refractory disease after initial therapy with paclitaxel-platinum should be offered investigational treatments or treatment with second-line drugs. Neither topotecan, oral etoposide, gemcitabine or any of the other drugs active in phase II studies can be considered the "drug of choice" for paclitaxel-platinum-resistant patients since all appear similarly effective.

Sensitive recurrent disease
The longer the treatment free interval, the higher the chance of response. For patients with their first recurrent ovarian cancer and a treatment-free interval between 4-12 months, there is no evidence that rechallenge with initial treatment is superior to using other second-line agents, such as topotecan, oral etoposide, or gemcitabine. Patients who had "sensitive recurrent disease," defined as having a progression-free interval of more than 12 months after initial platinum-based chemotherapy, may respond to a rechallenge with the initial treatment or can be retreated with either single-agent carboplatin or single-agent paclitaxel.

Routine use of serum CA 125 levels
There was general agreement that there was no evidence that the routine use of serum CA 125 levels in the follow-up of patients with ovarian cancer following initial chemotherapy was beneficial. Concern was expressed that routine monitoring of serum CA 125 levels following initial therapy was associated with unnecessary emotional stress without any evidence that acting upon an elevated CA 125 level improved survival or quality of life. It was also recognised that many patients are, however, followed with serum CA 125 levels at the time they finish their induction chemotherapy. There was uniform agreement that there was no established role for the immediate institution of cytotoxic chemotherapy in patients who had a serological relapse, defined as having a progressive rise in the serum CA 125 levels in an asymptomatic patient with a normal pelvic examination and without objective evidence of disease on radiologic studies. It was agreed that the randomised trial in progress by the MRC and EORTC should provide objective evidence regarding any potential benefit for use of chemotherapy in this situation.

High dose chemotherapy with stem cell support
High dose chemotherapy is not appropriate in patients with recurrent disease or primary refractory disease.

Research recommendations

Patient characteristics and end point assessment
Patients who are considered suitable for second-line therapies should be encouraged to receive treatment within the context of clinical trials. Characteristics that predict for both response and survival to second line therapy should always be reported in phase II studies. These include performance status, residual disease, treatment free interval, histology and number of sites of disease.

In the future, CA 125 may prove to be a valuable surrogate end point for response in phase II trials [16]. Further data are required to assess whether CA 125 progression is a valuable surrogate for standard time-to-progression in the context of comparative studies. In this setting, if CA 125 is to be used, precise definitions of CA 125 re-

sponse and progression are necessary for this end point to be of value (see above).

New drugs

There are a number of old and new cytotoxic agents which have been shown to be active in well evaluated phase II trials. These include etoposide, hexamethylmelamine, anthracyclines (liposomal doxorubicin), topotecan, gemcitabine, Taxotere, vinorelbine and oxaliplatin. These agents appear to have similar activity of approximately 20% in patients who relapse within 12 months; the main challenge with these compounds is to develop a methodology that will help decide which to take into first line and how to introduce them into the current standard regimens. Preclinical data need to be generated to help the design of these new combinations and to assist with the interpretation of the results. Response rate remains an appropriate end point although progression-free survival may also be used to reject a new combination.

New non-cytotoxic strategies include agents designed to circumvent drug resistance, signal transduction inhibitors, new hormonal agents, matrix metalloprotease inhibitors, gene therapy, and immunotherapy. Some of these strategies present novel difficulties in trial design and interpretation; response end points are difficult to evaluate and therefore it might be more appropriate to study biological effects.

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